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Incidence, prevalence and regional distribution of systemic sclerosis and related interstitial lung Disease: A nationwide retrospective cohort study

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Abstract

Objective: To investigate incidence and prevalence of Systemic Sclerosis (SSc) and association with interstitial lung disease (SSc-ILD) in a nationwide population-based study.

Methods: Patients with an incident diagnosis of SSc in 2000–2016 were identified in the Danish National Patient Registry and categorised based on diagnosis of ILD. Incidence- and prevalence proportions were calculated based on the annual population estimates. A cox proportional hazards model was used to evaluate the association between age, sex, region and marital status and presence of ILD.

Results: In total, 1869 patients with SSc were identified; 275 patients (14.7%) had SSc-ILD. The majority of patients were females (75.5%). The percentage of males was higher in SSc-ILD than in SSc alone (30.9% and 23.4%, $p = 0.008$). Median time from SSc to ILD diagnosis was 1.4 years (range 0–14.2). ILD was diagnosed from ≤4 years before to ≥7 years after SSc. Development of ILD was associated with male gender (HR 1.75, 95% CI 1.15–2.66), age 41–50 (HR 1.81, 95% CI 1.07–3.05) and residency in the North Denmark Region (HR 1.95, 9 5% CI 1.12–3.40). Mean annual incidence proportion of SSc was 2.9/100,000 and mean annual prevalence proportion was 16.8/100,000. The incidence remained stable, but prevalence proportion increased from 14.1 – 16.5/100,000 in 2000–2008 to 17.9–19.2/100,000 in 2009–2016.

Conclusion: The prevalence of SSc increased during the study period, while the incidence remained stable. The prevalence of SSc-ILD was 14.7% and thus less frequent than expected. Male sex and age between 41 and 50 years were associated with ILD.

Keywords

Systemic sclerosis, interstitial lung disease, incidence, prevalence, geographical distribution, epidemiology

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Introduction

Systemic Sclerosis (SSc) is a rare and complex autoimmune disease characterized by vascular inflammation, vascular hyperreactivity and excess collagen deposition in the tissue leading to vasculopathy and to fibrosis of the skin and internal organs.[1–3] The incidence proportion of SSc varies from 0.6–5.6/100,000 and the prevalence from 3.8–47/100,000[4–10] due to differences in investigated cohorts, countries, classification criteria, and methods used. Nevertheless, several studies and systematic reviews have described increasing incidence and prevalence of SSc over time.[4,5,11]

The first three to 5 years after SSc diagnosis are important for the prognosis as disease progression with organ involvement is frequent in this period.[12] Pulmonary involvement with interstitial lung disease (SSc-ILD) and pulmonary hypertension are common complications to SSc and associated with a high mortality.[13,14] Although most patients with SSc-ILD have stable disease or slow disease progression, some patients present with rapid lung function decline, usually within the first 3 years after ILD diagnosis.[15,16] Early diagnosis of SSc-ILD and regular follow-up is crucial, as early treatment initiation in case of disease progression may reduce lung function decline[17] and improve overall outcome.[18] Main risk factors for SSc-ILD are male sex, high baseline Rodnan skin score, diffuse cutaneous SSc (dcSSc), and positive anti-topoisomerase I antibodies.[19]

It is recommended that patients with SSc are followed at specialized centres.[20] In Denmark, management of SSc is centralized at three centres with collaborating rheumatologists, dermatologists, radiologists and pulmonologists, that follows national speciality plans.[20] The Health Care System in Denmark is tax-financed, and the majority of health care services are provided free of charge. The country is divided into five regions with regional authorities responsible for health care (Figure 1).[21,22] The regions differ with respect to population density, distribution and size of cities and rural areas, economy and distance to tertiary health care centres.

Data on geographical differences in distribution of SSc over time, prevalence of SSc with and without ILD and the timing of ILD diagnosis in relation to a diagnosis of SSc (before as well as after SSc diagnosis) are sparse. We therefore conducted this study using population-based health care data to provide a detailed overview adding to existing data from the same databases.[23]

Methods

Data sources

Information about primary and secondary diagnoses related to hospital contacts was extracted from the Danish National Patient Registry (DNPR) based on the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10).[24] Date of birth, place of residence, marital status and vital status were extracted from the Danish Civil Registration system.[25] Statistics Denmark provided information about educational level. The Central Person Registry-number assigned to all Danish residents enabled individual-level linkage across registries. The completeness of the national registries ensured complete follow-up regarding migration and mortality.[26,27]

Study population

The study population consisted of all patients above 18 years of age, resident in Denmark with a first-time diagnosis of SSc (ICD-10 code M34) in the DNPR in 2000–2016.

The SSc population was categorised into patients without a diagnosis of ILD (non-ILD SSc) and patients with a diagnosis of ILD in the DNPR at any time in the study period (SSc-ILD) (ICD-10 code J84).

Incidence proportion

The annual incidence proportion was defined as the number of new cases of SSc per 100,000 inhabitants per year in 2000–2016. To ensure reliable incidence data, patients with a previous SSc diagnosis in 1998–1999 were excluded.

Prevalence proportion

The annual prevalence proportion was defined as the number of patients with SSc, who had minimum one annual in- or outpatient hospital contact for SSc per 100,000 inhabitants. Prevalence proportion included all patients with a DNPR diagnosis of SSc at any time before and in the study period. According to national speciality plans, patients with SSc are seen in hospital settings and have minimum one annual follow-up.[20]

Statistical analyses

Mean annual incidence- and prevalence proportion were calculated using data from Statistics Denmark on individuals aged 18 years or older.[28] The interval between SSc and SSc-ILD diagnosis was presented as median values and Pearson's χ^2 test was used for comparison of categorical data. A Cox proportional hazards model was used to evaluate the association between time to development of ILD in patients with SSc and the covariates sex, age-group, marital status, and region of residence. In the Cox hazard model adjustment was performed for the covariate variables.[29] All cases with an ILD diagnosis are included for the whole period before and after SSc-diagnosis except in the

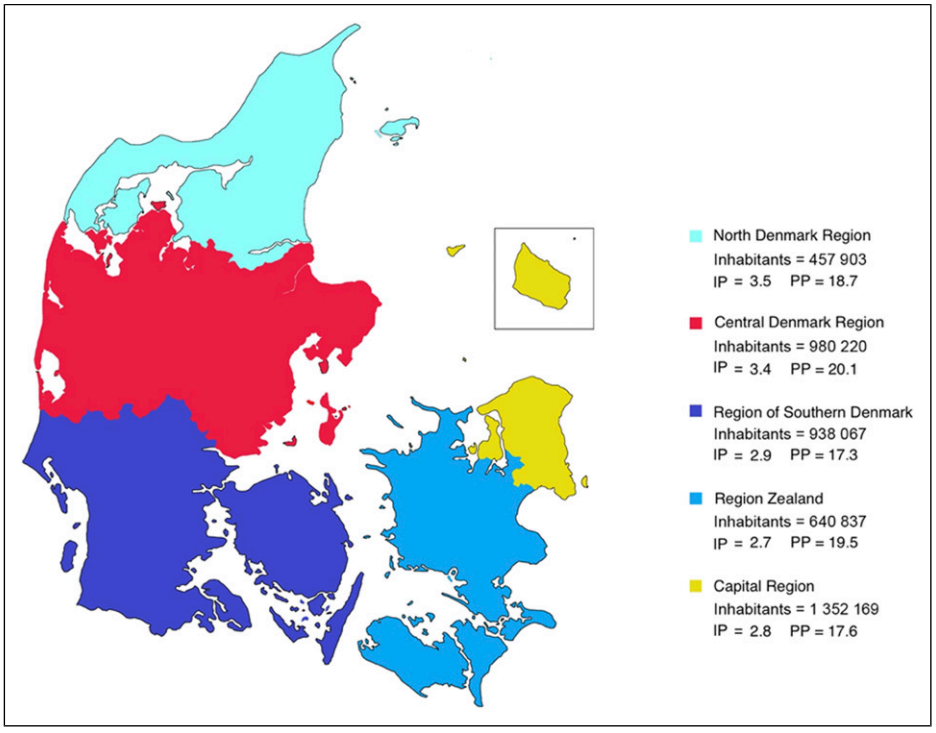

Figure 1. Regional map of Denmark showing mean number of inhabitants ≥18 years of age, mean annual incidence proportion (IP) (new SSc cases per 100,000 inhabitants) and mean prevalence proportion (PP) (number of SSc cases with minimum one hospital-contact for SSc per 100,000 inhabitants) in each region in 2008–2015. * One centre covers the North Denmark Region and the Central Denmark Region, one centre covers the Region of Southern Denmark and one centre covers Region Zealand and the Capital Region.

cox proportional hazard model, where only cases with an ILD diagnosis after an SSc diagnosis were included. A significance level of <0.05 was assumed for all tests. Statistical analyses were performed using SAS 9.4 (SAS, Inc., Cary, NC, USA).

Ethical considerations

The study was approved by the Danish Data Protection Agency. Data was extracted and approved by Statistics Denmark in anonymised form, and results with less than 5 cases were not reported as they may be personally identifiable. Ethical approval is not required for register studies in Denmark.

Results

Patient characteristics

During the study period, 1869 patients were diagnosed with SSc. Baseline demographics are shown in Table 1. SSc-ILD was diagnosed in 275 patients (14.7%). Mean age at the time of SSc diagnosis was similar in the two cohorts (56.7 years (SD 15.3) in non-ILD SSc and 57.7 years (SD 13.0) in SSc-ILD). Significantly more patients in the non-ILD SSc group were diagnosed with SSc before the age of 40 than in the SSc-ILD group ($p = 0.004$). The majority of patients were women with female:male ratio 3.3:1 in non-ILD SSc and 2.2:1 in SSc-ILD. Significantly more patients with SSc-ILD than non-ILD SSc were males (23.4% non-ILD SSc and 30.9% SSc-ILD ($p = 0.008$)). No difference was seen in marital status and level of education.

There were between 38 and 50 cases of SSc/100.000 inhabitants in the five regions of Denmark in the study period, and the frequency of SSc-ILD varied between 4.7–8.3/100.000. (Table 1).

Incidence and prevalence

The mean annual incidence for SSc was 126 (Supplementary table 1), and the mean annual incidence proportion was 2.9/100,000 (supplementary table 2 and Figure 2). During 2000–2016 the mean annual prevalence of SSc in Denmark was 722 (Supplementary table 1). An increasing prevalence was observed over time with an SSc prevalence proportion of 14.1–16.5/100,000 in 2000–2008 and 17.9–19.2/100,000 in 2009–2016 and a mean annual prevalence of 15.1/100,000 in 2000–2008 and 18.6/100,000 in 2009–2016 (Figure 2 and Supplementary table 2).

The mean annual SSc incidence proportion in the regions was between 2.6 and 3.6, and the mean annual SSc

Table 1. Number and prevalence of patients with SSc in 2000–2016 categorised by age, sex, marital status, region of residence and level of education. Data is shown for all SSc patients and separated in patients with SSc-ILD and non-ILD SSc.

	All SSc patients			non-ILD SSc			SSc-ILD		
	N	Prevalence	N/100.000	N	Prevalence	N/100.000	N	Prevalence	N/100.000
Total	**1.869**		**1594**		**275**				
Age									
18-40	292	15.6		265	16.6		27	9.8	
41-50	316	16.9		260	16.3		56	20.4	
51-60	462	24.7		392	24.6		70	25.5	
61-70	455	24.3		382	24.0		73	26.5	
>70	344	18.4		295	18.5		49	17.8	
Sex									
Male	458	24.5		373	23.4		85	30.9	
Female	1.411	75.5		1221	76.6		190	69.1	
Marital status									
Married	1.179	63.1		996	62.5		183	66.5	
Not married	690	36.9		598	37.5		92	33.5	
Region									
Capital Region of Denmark	525	28.1	38.3	452	28.4	33.0	73	26.5	5.3
Central Denmark Region	492	26.3	49.7	413	25.9	41.8	79	28.7	8.0
North Denmark Region	203	10.9	44.1	165	10.4	35.8	38	13.8	8.3
Region Zealand	253	13.5	39.2	223	14.0	34.6	30	10.9	4.7
Region of Southern Denmark	396	21.2	42.0	341	21.4	36.1	55	20.0	5.8
Education									
Primary	661	35.4		558	35.0		103	37.5	
Secondary	88	4.7		76	4.8		12	4.4	
Vocational	666	35.6		565	35.4		101	36.7	
Short college	52	2.8		46	2.9		6	2.2	
Medium college	275	14.7		237	14.9		38	13.8	
Master/PhD	75	4.0		63	4.0		12	4.4	
Unknown	52	2.8		49	3.1		<5	-	

prevalence proportion was comparable across regions at 16.76–19.81/100.000. (Supplementary table 3 and Supplementary figure 1).

Diagnosis of ILD

Among patients with SSc-ILD, ILD was diagnosed within 1 year before or after SSc in 53.8% and within 3 years in 74.5%. The median time from SSc diagnosis to ILD diagnosis was 1.4 years (range 0–14.2 years). In 35.3% of cases, the diagnosis of ILD preceded the diagnosis of SSc (Figure 3).

A multivariate Cox proportional hazards model with adjusted covariates showed that male sex, age between 41–50 years and residency in the North Denmark Region were significantly associated with a diagnosis of SSc-ILD (Table 2).

Discussion

This nationwide, registry-based cohort study of SSc showed a stable mean annual incidence proportion and increasing prevalence proportion with uniform geographical distribution. The majority of patients with SSc were females, but males had a higher risk of SSc-ILD. SSc-ILD was diagnosed in fewer patients than expected and primarily within the first 3 years after SSc diagnosis. The median time from SSc to ILD diagnosis was 1.4 years. Male sex, age between 41–50 years and residency in the North Denmark Region were associated with development of SSc-ILD.

Patient characteristics

No difference was seen in the demographic characteristics for patients with SSc, who developed ILD compared with those who did not, including no difference in mean age at the time of SSc diagnosis (56.7 and 57.7 years, respectively) corresponding to previous findings in SSc in Denmark and in a large recent EUSTAR study.[23,30] The majority of patients were women, but a higher proportion of male patients had SSc-ILD, which is in line with previous findings.[4,23]

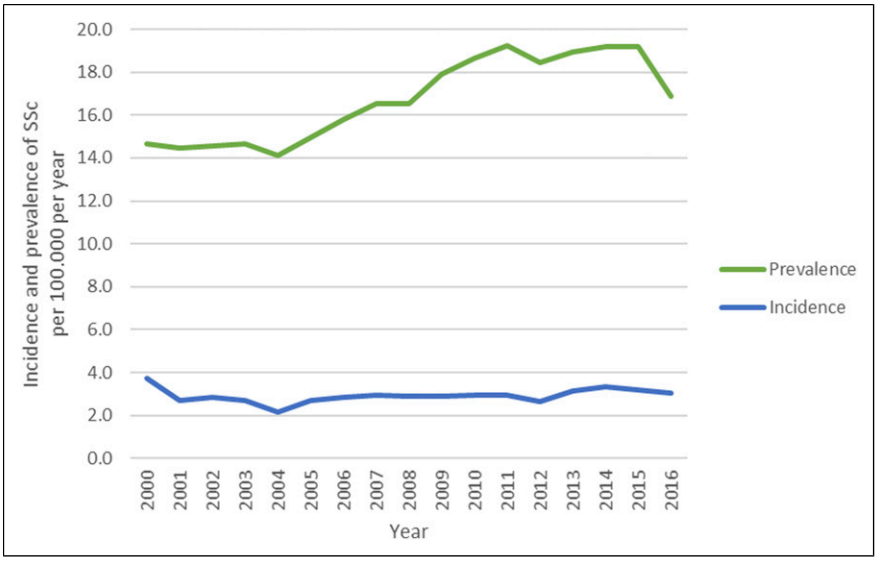

Figure 2. Annual incidence proportion and annual prevalence proportion of patients with SSc in the time period 2000–2016. Data is presented as number of patients with SSc (ICD-10 code M34) per 100,000 inhabitants per year.

Table 2. Mulitvariate Cox proportional hazards model showing association between time to development of ILD and sex, age-group, region of residence and marital status (adjusted covariates).

	HR (95 % CI)	*p*-value
Male sex	1.75 (1.15–2.66)	0.01
Age	1.00 (0.99–1.02)	0.63
18-40	1.00	
41-50	1.81 (1.07–3.05)	0.02
51-60	1.50 (0.90–2.49)	0.11
61-70 1.32 (0.78-2.21)	0.29	
70+	0.83 (0.45–1.54)	0.55
Married	1.06 (0.77–1.46)	0.72
Region		
Capital Region of Denmark	1.00	
Central Denmark Region	1.41 (0.89–2.22)	0.13
North Denmark Region	1.95 (1.12–3.40)	0.02
Region Zealand	0.76 (0.44–1.32)	0.33
Region of Southern Denmark	1.05 (0.66–1.67)	0.86

HR: hazard ratio; CI: confidence interval . The Capital Region of Denmark was used as reference.

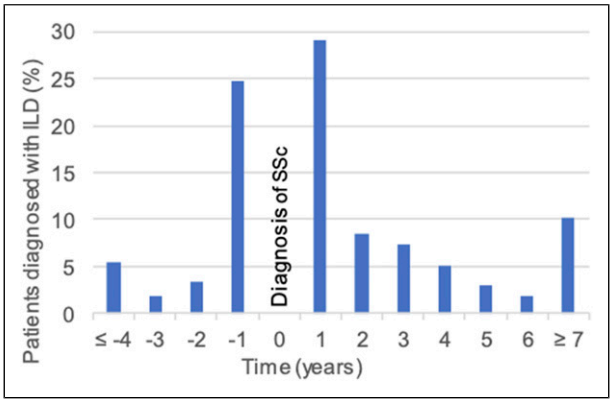

Figure 3. Relation between the time of SSc diagnosis and the time of ILD diagnosis. SSc was diagnosed at time 0. The columns show the percentage of patients diagnosed with ILD each year before and after SSc diagnosis. Due to low numbers, ILD diagnosis 4 years before and 7 years after SSc are summed.

More patients with non-ILD SSc than SSc-ILD were diagnosed with SSc at a young age.

Incidence and prevalence

Our study shows a stable mean annual incidence proportion of SSc at 2.9/100,000. The mean annual incidence proportion in our study was higher than described in a previous Danish study and two European studies reporting an overall incidence at 2.44/100,000 person-years[23] and 0.6–2.3/100,000.[5–7] Previous studies that only include individuals above the age of 18 report lower incidence, ranging from 0.8–1.9/100,000.[8,9] The high SSc incidence could be due to a high completeness of the national registries in Denmark,[26,27] but we cannot rule out the possibility that some patients may be misdiagnosed with SSc. However, the high SSc incidence in our study, does not support the theory of a North-South gradient with lower incidence in northern European countries than in southern European countries.[4,11]

The change in incidence and prevalence in 2016, particularly in the Capital Region of Denmark, may be caused

by the introduction of a new electronic patient record, Sundhedsplatformen, introduced over several months in the Capital Region of Denmark and in Region Zealand, causing some reduction in hospital activity in the first months after its introduction.[31] However, our data for 2016 were not significantly different from the preceding years and are not believed to affect the overall results. Additionally, the overall decline may be due to a related delay in the general registration of diagnoses in the DNPR.

The mean annual prevalence proportion increased over time from 15.1 in 2000–2008 to 18.6 in 2009–2016, corresponding to findings in previous studies.[4,5] The increasing prevalence may indicate gradually better survival among patients with SSc. This change may be due to better management and improved treatment options, or perhaps an element of lead time bias due to earlier diagnosis after the introduction of new diagnostic guidelines in 2013.[32] No increase was seen in the incidence of SSc after the update of the national speciality plans[20] and therefore we do not have concerns for confounding due to guideline changes.

Regional SSc incidence- and prevalence proportions demonstrated no difference across the country. Natural variation and difference in the size of the regions may explain the fluctuations seen in this study.

This is in accordance with previous findings in the UK,[33] whereas studies from Italy and Canada found higher prevalence in rural areas compared to urban areas.[34,35]

The uniform distribution of SSc across Denmark may be seen as an indicator of equivalent access to health care services, although there may still be regional differences, even in a small country, especially regarding access to specialists in rheumatology, dermatology and pulmonology as well as barriers related to distance to tertiary centres.

Diagnosis of ILD

The definition of ILD substantially affects the observed proportion of ILD across different studies. A Dutch study reported an ILD prevalence of 18.8–47.0% among patients with SSc based on TLC lower than 70% or fibrosis on HRCT.[8] Other studies report ILD proportions ranging from 32.3% in the UK[36] to 50% in Norway[37] and 52.3% in Canada.[38] The ILD diagnosis may be based on HRCT findings or lung biopsy as in the British study,[36] on multiple imputation without HRCT as in the Canadian study[38] or on baseline HRCT scans manually reviewed for signs of fibrosis as in the Norwegian study.[37] The frequency of ILD in our study was remarkably low compared to previous findings. Differences in incidence probably reflect difference in cohort selection rather than genuine differences in ILD frequency.[30,37] Our findings were based on register data, and are likely to reflect patients with clinically significant ILD. We expect a high validity of the actual registered ILD diagnoses, but patients with subclinical SSc-ILD may not be captured by ICD-10 diagnoses. Furthermore, some patients may have been misclassified with other respiratory diagnoses. According to the 2013 EULAR guidelines, signs of ILD on HRCT scan is among the classification criteria for SSc.[32] At present, there are no formal guidelines for ILD screening in SSc, but current clinical practice at the Danish centres, involves a screening like approach with HRCT scan at the time of SSc diagnosis and annual pulmonary function tests.

Most SSc-ILD patients were diagnosed within 1 year before or after SSc diagnosis demonstrating the high awareness among rheumatologists and pulmonologists of the possible concurrent presence of connective tissue disease and ILD.

In the present study, 74.5% of patients with ILD were diagnosed within 3 years before or after the SSc diagnosis corresponding with findings in previous studies.[16] In 35.3% of patients, ILD was diagnosed before SSc in accordance with previous findings.[39] However, 20% of patients with ILD in our cohort were diagnosed more than three years after the SSc diagnosis and 10.2% after more than 7 years. Previous findings demonstrate that patients with dcSSc are at greater risk of developing ILD and at an earlier time in life than patients with limited cutaneous SSc.[2,12,16] Due to the register-based nature of this study with no clinical details available from the registry data, we cannot determine if certain subtypes of SSc in this cohort were associated with higher risk of ILD or had an earlier ILD diagnosis than others.

We found that the presence of ILD was associated with male sex, age 41–50 and residency in the North Denmark Region. To the best of our knowledge, there are no regional differences in the initial investigation of patients with SSc suspected for ILD, and the observed difference in the burden of ILD is difficult to explain due to the relative homogeneity of the population.

Strengths and limitations

The strengths of this study are its population-based cohort design, the comprehensiveness of follow up and the unique linkage across registries. Because the diagnoses of SSc and SSc-ILD are assigned in a tertiary setting and involves two specialties; and for ILD, often a multidisciplinary team conference, we assume a high positive predictive value of the ICD-10 codes. Butt et al. performed a validation study on the ICD-10 diagnosis of SSc by reviewing patient records and found a positive predictive value of 94%.[23]

It is a limitation to the register study that the ILD diagnosis, J84, includes several subtypes of ILD, and the data does not provide information about the type of ILD or the relation with SSc. It is reasonable to assume that this had minor influence on our results, since other subtypes of ILD unrelated to SSc, are rare. There exists no validation study

of the ILS diagnosis in the Danish national registries which could potentially lead to misclassification bias. However, using national registries within a uniform health care system reduces the risk of selection bias. We cannot determine causation between e.g. SSc and ILD, only association due to the retrospective study design. Patients with mild or subclinical ILD may not be registered, or in some cases remain undiagnosed. The threshold for assigning the ILD diagnosis may vary between centres, and, in line with this, the optimal management of subclinical disease is unclear.

Conclusion and future implications

This study showed increasing prevalence proportions of SSc with uniform geographical distribution across Denmark with stable incidence proportions, pointing towards improved diagnostics, improved outcome in SSc and longer survival. The majority of SSc-ILD patients were diagnosed with ILD within 3 years after the SSc diagnosis showing a high clinical awareness of the association between SSc and ILD. Male sex, age between 41 and 50 years and region of residence was associated with the presence of ILD underlining the need for special attention to the risk of ILD in this group of patients with SSc.

Authors contributions

MK, CH, EB, JRD, AL, SBS and OH all contributed to the planning and design of the study. AL and RI had full access to data and take responsibility for the integrity of the data and the accuracy of the data analysis. Statistical analyses were performed by RI. The first draft of the article was written by MK with input and critical revision from AL, EB, JRD, CH, SBS and OH. All authors revised the manuscript and approved the final version. All authors take responsibility for the integrity of the work as a whole, including the data and analyses.

Declaration of Conflicting Interests

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Submission declaration

This work has not been published previously and is not under consideration for publication elsewhere. If accepted for publication, the work will not be published elsewhere in the same form. Publication has been approved by all authors.

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Supplemental Material

Supplemental material for this article is available online.

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